Updating hippocampal representations: CA2 joins the circuit

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Abstract

The hippocampus integrates the encoding, storage and recall of memories, binding the spatio-temporal and sensory information that constitutes experience and keeping episodes in their correct context. The rapid and accurate processing of such daunting volumes of continuously-changing data relies on dynamically assigning different aspects of mnemonic processing to specialized, interconnected networks corresponding to the anatomical subfields of dentate gyrus (DG), CA3 and CA1. However, differentially processed information ultimately has to be reintegrated into conjunctive representations, and this is unlikely to be achieved by unidirectional, sequential steps through a DG-CA3-CA1 loop. In this Review, we highlight recently discovered anatomical and physiological features that are likely to necessitate updates to the hippocampal circuit diagram, particularly by incorporating the oft-neglected CA2 region.

Introduction

Adaptations of the hippocampus likely to reflect the demands of memory processing are immediately apparent in its gross histology: the dense hippocampal cell layers are precisely arranged in a circuit of subfields encompassing the arrowhead of dentate gyrus (DG) and the curve of CA1-3. No single, homogeneous neural network can process all aspects of episodic memory simultaneously, and indeed anatomical, neurophysiological and behavioural studies over the past two centuries or more have informed influential models of these subfields as specialized processing modules, each contributing to different facets of hippocampal function.

In piecing together this jigsaw of hippocampal subfields and connections, the collective tendency has been to start with the DG and build around a trisynaptic circuit to CA3 and then CA1 (Figure 1a,b). Most models emphasize sequential steps of information processing in this circuit: layer II principal cells of the entorhinal cortex (EC) project to the granule cells of the DG through the perforant path (PP), the granule cells project to CA3 pyramidal cells through mossy fibers (MF), CA3 pyramidal cells synapse onto CA1 pyramidal cells via the Schaffer collaterals (SC), then CA1 outputs to subiculum, deep-layer EC pyramidal cells and related parahippocampal and frontal neocortical regions. Prominent examples of differential information processing include pattern separation in DG (granule cells are abundant and sparse-firing, hence different patterns of EC inputs are highly unlikely to activate identical subsets of granule cells and may be 'orthoganolized' at this stage) followed by pattern completion in CA3 (where dense recurrent, excitatory projections within its own pyramidal cell population endow 'auto-associative' properties) [1-5](see also [Ref] in this issue). The neat

hippocampal loop has therefore been presumed to allow integration and processing of information provided via association cortex, then subsequent feedback to the cortex via CA1.

However, as the resolution of anatomical knowledge reaches the sub-cellular level and the nature of hippocampal network activity during a diverse behavioral repertoire of encoding, processing, storage and recall is increasingly well documented, simplifying models inevitably become more complex (see Box 1). Here, we review recent discoveries likely to necessitate updates to the prevailing hypotheses, with particular emphasis on the potentially unique contributions made by the oft-neglected subfield, CA2.

Coding the spatial context of memories

As in humans, the hippocampi of non-human animals play crucial roles in the memory of where, when and what aspects of events [6-9] and their relative positions in space and time [10]. The rodent hippocampus in particular has proved a powerful model in which to test numerical and computational aspects of memory using anatomical and functional studies respectively. Multi-neuron recordings pioneered in behaving rodents have uncovered the nature of information processing in different hippocampal regions by defining the behavioral-dependence of the firing rates and patterns of their constituent principal cells. Using this approach, it was demonstrated that single CA1 neurons increased their action potential firing rate whenever a rat traversed a particular region of an environment, dubbed the cell's place field; this prompted the hypothesis that these place cells constitute the neural substrate of a cognitive map [11]. In concert with data demonstrating that hippocampal damage impairs spatial learning [12], place cells provided a link from neural spiking to behavior. By recording

from large numbers of cells simultaneously, subsequent studies have provided evidence that place cells can represent memory traces at the neuronal ensemble level [13-21], and are therefore a compelling electrophysiological correlate of a natural form of learning in freely-behaving animals. Importantly, a growing body of human electrophysiological and imaging data appears to support models based on rat and mouse findings [22-24].

The discovery of place cells raised an enduring question: is spatially-modulated neural activity generated within the hippocampus, or does it culminate from hippocampal integration of spatially-modulated input? Over the past decade, comprehensive examination of the coding properties of neurons in the EC has uncovered a considerable amount of *where* information upstream of the hippocampus. The most striking and insightful discovery relates to the firing properties of grid cells, a subset of spiny stellate and pyramidal principal neurons in medial EC (MEC) layers II and III that project to the dorsal hippocampus. The spatial receptive fields of these neurons reflect a striking 2-D coordinate system arranged in hexagonal grids spanning the environment [25]. Grid cell firing is therefore uniquely well-placed to provide a metric of spatial location and distance moved; this information is projected, directly and indirectly, to all hippocampal subregions [26, 27].

Some quirks of entorhinal-hippocampal connectivity

In the superficial MEC, grid cells in layer III differ from those in layer II in that many (~66%) also convey information regarding the direction the animal is heading [ie. head direction (HD)] [28]. In addition to these conjunctive cells, MEC layer III also contains HD cells similar to those found in thalamic, subicular and retrosplenial regions [29-31]. Finally both layers II and III contain

border cells, which respond to edges of a local environment and have been suggested to anchor the grid and place cells to a common frame of reference [32, 33]. These predominantly spatial determinants of MEC grid cell firing are quite distinct from those in lateral EC (LEC), which does not contain grid or HD cells but rather neurons that predominantly respond to non-spatial, object-related information, presumably contributing to other aspects of episodes [34, 35] (Figure 1c). LEC also appears to be set apart by a reduced predominance of population theta oscillations relative to MEC [36], although the mechanisms through which non-spatial information conveyed via LEC is integrated within the hippocampus to form conjunctive spatiotemporal representations incorporating *what* and *where* remain largely unproven. Nevertheless, it is clear that firing rates in the MEC preferentially and comprehensively encode parameters encompassing location, direction and boundary. How is this information conveyed to the hippocampus, giving rise to the spatial firing properties of hippocampal place cells which are evident throughout DG and CA subfields?

Various models have been proposed, most suggesting that place fields can emerge from summation of input from grid cells with different orientations and spatial scales [37-39]. However, each hippocampal subfield receives a unique combination of projections from the EC, and each presumably contributes differentially to the processing and integration of spatial information (Figure 1). Information at different stages of processing may therefore converge upon different subregions at different times. The wiring of the hippocampal circuit diagram and – setting aside non-spatial LEC input – its relationship to the spatial coding properties of hippocampal neurons provides important clues as to how this drives activity in CA1 and culminates in hippocampal output.

Hippocampal connections with the EC provide numerous direct and indirect routes and shortcuts around the trisynaptic circuit (reviewed in [40]). Based on anatomy, it is very likely that the grid and border cells in EC layer II project directly to DG as well as CA3 via the PP; grid, HD and border cells in layer III EC project directly to CA1 through the temporoammonic pathway (TA); and projections from both layer II and III neurons converge on the pyramidal cells of CA2 [41] (Figure 1). However, deep EC layers also contribute to PP projections [40], and only cellular-level connectomics will establish the extent to which projections from different EC subpopulations converge and diverge at their hippocampal targets.

Further complicating matters, the superficial and deep layers of EC are directly connected with one another intra-cortically, in microcircuits recently reported to differentially impact layer II stellate and layer II/III pyramidal cells [42]. While the functional ramifications of reentrant EC-hippocampal loops are not yet fully understood, they make defining and decoding the critical elements of such a massively interconnected and reciprocal network challenging. However, in a circular system where the start and endpoint cannot be categorically defined, it seems likely that hippocampal subregions able to act as gates or filters – thereby dynamically directing information flow and mediating convergence and comparison of different combinations of raw and processed spatial information – are likely to be key.

CA2 comes in from the cold

Since its definition on the basis of lack of mossy fiber input or thorny excrescences [43], CA2 has been quietly ignored for the most part, and has been notably absent from the vast majority of hippocampal circuit diagrams and models. However, building on the small existing literature,

recent studies have begun to establish a unique connectivity and physiology consistent with CA2 being far more than a passive transition zone between CA3 and CA1.

The borders of rodent CA2 with enveloping CA3 and CA1 are delineated somewhat by selective afferentation by the supramammillary nucleus of the hypothalamus [44, 45] and sparse innervation by nucleus reuniens of the thalamus relative to CA1 [46, 47]. The gene expression profile of neurons within CA2 (Box 2) is also increasingly well understood [48], and includes preferential expression of vasopressin 1b receptors [49] and strikingly selective expression of adenosine A1 receptors [50], fibroblast growth factor 2 (FGF-2) [51] and the Regulator of G-protein Signaling 14 (RGS14) [52]. Combining these anatomical and proteomic signatures therefore enables objective identification of CA2's extent that can be used to target functional and physiological studies.

Although the neurophysiology of CA2 is largely uncharted, studies to date have been quick to highlight its unique status. For example, both optical imaging in slices [53] and *in vivo* electrophysiology [54] highlight CA2 responses inconsistent with sequential activation as part of the trisynaptic loop. Further, Schaffer collateral synapses onto CA2 pyramidal neurons do not exhibit experimentally-induced plasticity as readily as those in CA1 or CA3 [55], potentially because of increased spine calcium buffering [56]. CA2 interneurons and their synapses with local pyramidal cells also show unique physiological signatures [57, 58], which suggest that CA2 can inhibit CA3 and CA1 in a feedback and feed-forward manner, respectively.

An important and potentially influential role for CA2 in hippocampal function was recently suggested [41]. Whole-cell recordings from CA2 pyramidal cells in acute slices of adult mouse

dorsal hippocampus showed that CA2 pyramids are distinct from CA1 in their dendritic morphology, connectivity and basal membrane properties (Figure 1c). However, none of these differences predict the stark difference in response to stimulation of CA3 or MEC input between these two CA subfields reported in this study: in CA1, the Schaffer collateral inputs from CA3 proved strong and highly plastic, while MEC III input (TA pathway) stimulation resulted in, at best, a weak excitatory response. These findings are most likely due to a combination of dendritic attenuation and feed-forward inhibition, though will also depend on the level of coincident Schaffer collateral input [59, 60]. In the CA2 neurons this was completely reversed: CA3 inputs were weak and stimulation often resulted in a net inhibition in CA2, whereas both the LII and LIII inputs from EC were found to be strong and highly plastic. Finally, in the same preparation it was demonstrated that stimulation of CA2 resulted in robust excitation of CA1 pyramidal cells, completing a new and potent route for information flow from the EC to CA1.

It is not clear whether previous studies suggesting that the TA pathway is an important modulator of CA1 function [61, 62] may have overlooked CA2's contributions. Regardless, the recently reported physiology and anatomy [41] suggest that CA2 may be the only hippocampal subregion in which the theta phase precessing grid and border cells of LII and the theta phase locked border, HD, conjunctive and grid cells LIII [63] converge and interact. Thus, in terms of MEC input, CA2 seems well-placed to integrate all available types of spatial, directional, movement and border information. The next logical question is how this might be reflected by CA2's functional contributions?

Selecting circuits within circuits: who does what, when?

Clues to deciphering CA2 function can be gleaned from interventional studies, some aimed specifically at CA2 and others targeting CA3 (see also Box 2). Mice lacking the Avpr1b gene, which encodes the vasopressin 1b receptor that is enriched in – although not restricted to – CA2 pyramidal cells demonstrate intact spatial learning [64], but impairments in two tasks related to the memory of temporal order [65]. Unfortunately, the physiological impact of the mutation was not determined. Mutant mice lacking the CA2-enriched protein RGS14, which is involved in H-Ras/Mitogen-activated protein kinase (MAPK) signaling, demonstrated enhanced spatial learning and enhanced long-term potentiation (LTP) at the CA3-CA2 synapse [52]. Together, these studies suggest possible roles of CA2 in linking time and space, and are consistent with a potential role for CA2 in differentially routing information to CA1.

There are no reports of explicitly targeted *in vivo* recordings of CA2 activity to date, and a tendency to equate CA2 and CA1 place cell properties (e.g. [66]). As such, future work should certainly aim to quantify behaviorally mediated spatial transformations unique to this region. Based upon the *in vitro* physiology described above, CA2 is most likely to be engaged when net drive from CA3 (and therefore net feed-forward inhibition of CA2) is low, and *vice versa*. This provides a hypothetical basis for switching between CA1's links to EC via DG-CA3 or CA2 routes at different times, either on a sub-second timescale during theta oscillations [67, 68] and/or during different behavioral states (Figure 2). There is certainly evidence based on stimulation experiments that shortcuts around the trisynaptic circuit mean EC input can bypass DG and/or CA3 [69, 70], although the contribution of CA2 to these shortcuts has yet to be determined. It should be noted, however, that network dynamics during behaviour cannot always be directly

predicted on the basis of pathway mapping using stimulation-evoked responses, particularly in isolated slice preparations or under anesthesia.

In freely-behaving animals, distinct EC-hippocampal single unit and local field potential patterns differentiate encoding (e.g. during exploration of a novel environment), consolidation (eg. off-line activity, such as occurs during sleep) and recall (e.g. recognition of a familiar environment) (Figure 2). During active exploration and encoding of novel spatial information, rodent MEC and dorsal hippocampal principal cell and interneuron populations are dominated by theta rhythmic, oscillatory activity at 4-12 Hz (see [71]). Theta rhythms recorded in different subregions are covariant during active behavior [72], but the precise nature and behavioral-dependence of underlying cell pair interactions spanning DG, CA3 and CA1 remains to be established. Theta rhythmicity is associated with phase-locking and phase precession of neuronal spiking, and thereby imposes complex timing relationships typically not evident *in vitro*. For example, theta phase precession is more prevalent in MEC LII than LIII [63]. It is not yet known what impact this has on LIII-CA1 and LII/LIII-CA2 interactions and the potential recruitment of hippocampal cell assemblies by EC input [73]. However, the nature of spatial coding during different conditions presumably reflects behavior-dependent routing of information, and coordination of oscillations across different subregions during different behavioral stages of learning and memory is likely to be key (Box 3).

Place fields in CA1 and CA3 are slightly less spatially tuned and considerably less stable in novel *versus* familiar environments [74]; this may indicate that CA1 activity is dominated by direct, rapid, but unprocessed EC-CA2 input under these conditions, whereas slow refinement of CA1

spatial coding over days [75] relies on CA3-DG-CA1 processing; some lesion data are consistent with this. For example, knife cuts between CA3 and CA1 did not impair rats in a spatial learning task and resulted in CA1 place fields only slightly larger than those of the control rats [76]. Since lesion of direct EC-CA1 inputs did impair spatial coding [77], these studies were taken to suggest that the animals do not entirely depend on the integrity of the trisynaptic loop and SC input for acquisition or recall of spatial information, and that direct EC-CA1 input may be sufficient to underpin spatial learning and coding. However – depending on how CA2 was impacted by these lesions –these data could be reinterpreted to include a role for CA2 in supporting CA1 place cells in the absence of DG-CA3 mediated processing.

Similarly, mice with inducible and reversible silencing of CA3-CA1 transmission were able to perform normally in a reference memory version of the Morris water maze [78]. This again suggests that this type of learning can be achieved in the absence of any DG-CA3 contribution to CA1 excitation, although further experiments are necessary to address whether this remaining spatial learning requires CA2 activity. At the physiological level, place field recordings from the CA1 region of these mice identified a strong phenotype in the absence of CA3-CA1 transmission [78]: in a novel environment CA1 place fields were present, however the spatial specificity of individual cells was significantly poorer than control neurons and firing rates were elevated, which may again reflect CA2-CA1 rapid-but-inaccurate routes. It has also been reported that there is a slowing of the frequency of the theta rhythm in CA1 in novel environments [79]. Taken together with the fact that the hippocampus has multiple theta generators, perhaps reflecting input to the individual subfields [72], it will be interesting to see if CA2 contributes to behavior-dependent theta frequency shifts. This may be enabled by

novelty-dependent activation of projections from the supramammillary (SuM) nucleus of the hypothalamus, which selectively innervates CA2 and the upper blade of dorsal DG [80, 81].

In contrast to theta states, it is established that during the sharp wave/ripple events which dominate the hippocampal network during quiet immobility and slow-wave sleep, CA3 provides relatively strong excitatory drive to CA1 [82]. Structured ensemble activity during these events is thought to underlie memory consolidation during sleep [83], and may also contribute to rapid processing underpinning consolidation or refinement of encoding during learning itself [84, 85]. If CA2 is indeed suppressed when CA3 drive is high, this suggests CA2 does not actively participate in memory consolidation (note, however, that mice with silenced CA3-CA1 transmission do still show ripples in CA1 [86] – whether CA2 contributes to these remains unresolved).

As mentioned above, one of the proteins highly expressed in CA2 pyramidal cells is the adenosine A1 receptor [50]. Adenosine is a byproduct of ATP metabolism and its levels increase throughout the active phase of the circadian cycle, peaking before sleep onset (see [87]). Thus, one possibility is that A1 receptors may mediate inhibition of CA2 output when adenosine levels are high [81] and assist in taking CA2 off-line, weighting the hippocampal network towards CA3-CA1 mediated memory consolidation following sustained wakefulness (Figure 2b). It is also feasible that CA2 contributes to reported alterations of excitability and plasticity in CA1 following sleep deprivation [88]. Thus, CA2 may contribute to differential routing of information through hippocampal circuits, which may shift on timescales spanning

seconds to hours. The presence of A1 receptors in the CA2 may also have important implications during disease states such as epilepsy, as discussed in Box 4.

Conclusions

The hippocampus is typically taken as a model of sequential processing in the nervous system, with a chain of specialized subfields each contributing to different aspects of episodic memory function. While this is broadly consistent with place cell data relating to encoding of spatial information, views of the trisynaptic loop through DG, CA3 and CA1 need updating, particularly by incorporating CA2, to accommodate a wealth of new anatomical, genetic and physiological data. Anatomy dictates that hippocampal processing can propagate through four alternative and overlapping loops: (1) the trisynaptic loop involving DG, CA3 and CA1; (2) a disynaptic loop involving CA3 and CA1; (3) a disynaptic loop involving CA2 and CA1, and (4) the monosynaptic TA pathway involving only CA1. The emergent properties of these distinct but co-dependent circuits are likely to depend on the dynamic, behavior-dependent routing of activity - experiments explicitly targeting recordings and interventions to CA2 will be required to unmask CA2-specific roles in this routing and their consequent function contributions (Box 5).

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Figure legends

Figure 1. Circuits and space from the EC to CA1. Schematic routes for spatial information from the superficial layers (II/III) of the medial entorhinal cortex (MEC) and less spatially-specific information from the lateral entorhinal cortex (LEC) into the four anatomically distinct subregions of the hippocampus: the dentate gyrus (DG), area CA3, area CA2 and area CA1. Thick arrow in CA3 represents the recurrent network; circuits are distinguished by color (MF-mossy fibers, SC-Schaffer collaterals). **(a)** Two largely overlapping circuits from layer II of the EC via the perforant path (PP): the trisynaptic loop (red arrows) involving DG, CA3 and CA1 and a disynaptic loop involving CA3 and CA1 (purple arrows). **(b)** Two circuits originating in EC layer III: a disynaptic loop with convergent ECII/III input to CA2 (blue arrows) and the monosynaptic temporoammonic (TA) pathway (green arrows) from layer III direct to distal dendrites of CA1 pyramidal cells; note that in CA1 input from the MEC and LEC diverges to proximal (bordering CA2) and distal pyramidal cells respectively. **(c)** Spatial inputs (boxes alongside dendrites) and outputs (red boxes) of CA2 and CA1 pyramidal cells are represented as single cell firing rate maps showing top-down views of a 1m x 1m square environment with areas of high firing rate colored red and yellow and areas with no firing colored blue; head direction cells are represented by the x/y plot of angular firing. The position of the rate map indicates the location of the input on the pyramidal cell's dendritic tree, with the bar to the left marking different cellular and synaptic layers of the hippocampus (SO- *stratum oriens,* SP-*stratum pyramidal,* SR- *stratum radiatum*, SLM- *stratum lacunosum moleculare*). Listed in each box are the physiological and anatomical distinctions between the pyramidal cells of CA1 and CA2 [41].

Left panel: CA2 receives converging spatial input from CA3 (place cells), and both LII (grid cells, border cells) and III (border cells, grid cells, conjunctive cells, HD cells) of the MEC and non-spatial information from LII/III of the LEC; although evidence is scant [66], CA2 place fields are thought to be similar to the discreet fields observed in CA1. *Right panel:* CA1 pyramidal cells receive input in the SR from CA2 (place cell) and CA3 (place cell), in addition to CA2 input to SO dendrites. In CA1 there is a gradient of spatial responses across the proximal/distal access of dorsal CA1 [89, 90] that may reflect the underlying shift in projections from the spatial MEC input (border cells, grid cells, conjunctive cells, HD cells) in proximal CA1 to the non-spatial LEC input in the distal CA1.

Figure 2. Differential network interactions during encoding, consolidation and recall. In each panel the arrows represent excitatory inputs; active neurons are green and silent neurons black. The thick arrow in CA3 represents the recurrent network. Interacting regions are identical in color, with the color corresponding to circuits listed on the right of each figure. In the upper left of each panel is an example CA1 local field potential (LFP) trace with red ticks indicating the timing of CA1 pyramidal cell firing in relation to the LFP. **(a)** *Encoding*. During memory encoding the DG/CA3 network may operate as a pattern separator and activate a slowly crystallizing ensemble of CA3 pyramidal cells (e.g. [74]) via activation of the recurrent network. Inhibition in the DG dominates and helps to ensure a unique and sparse ensemble is activated. CA2/CA1 works independently to rapidly encode episodes in CA1 based primarily on direct input from EC. CA1's dependence on EC input is reflected by the physiology: overall

theta frequency in CA1 is slower [79], CA1 spikes prefer a later phase of theta [91] and more EC mediated fast gamma is observed [67]. **(b)** *Consolidation.* During off-line consolidation periods synchronous depolarization of CA3 pyramidal cells, made possible via the recurrent collaterals, generate high frequency ripple oscillations. Burst firing during ripples is associated with reactivation of recently encoded neuronal ensemble in both regions and allows the association of the CA3 and CA1 traces. CA3 feed-forward inhibition of CA2 limits its excitability during these rest periods, perhaps further facilitated by high levels of circulating adenosine serving to dampen CA2 activity. **(c)** *Recall.* During recall the recurrent collaterals of CA3 mediate pattern completion and memory-driven input excites CA1 via the Schaffer collateral inputs. Feedback inhibition from CA3 to DG limits DG activity. In CA1, theta oscillations are slightly faster during recall as compared to during encoding [79], as well as being coupled with the slow gamma oscillations observed in CA3 [67]. Additionally, place cell spiking in CA1 prefers a slightly early phase of theta [91].

Box 2, Figure I. *CA2 enriched gene expression.*

High-throughput *in situ* hybridization to visualize genes expressed in the mouse brain has enabled the CA subfields of the hippocampus to be distinguished at the molecular level. Transcripts enriched in CA2 pyramidal cells include (a) Regulator of G-protein Signaling 14 (Rgs14), (b) Purkinje cell protein 4 (Pcp4), and (c) Arginine vasopressin receptor 1B (Avpr1B).

(Allen Mouse Brain Atlas [Internet]. Seattle (WA): Allen Institute for Brain Science. ©2009. Available from: http://mouse.brain-map.org)

Box 1: Thinking in 3-D

It is commonplace to represent both the hippocampus (around its dorsal lamellar axis) and the space it represents (place fields) in two dimensions. However, anatomy, physiology, function [89 , 92-95] and indeed space itself [96-98] are three dimensional. Whilst the hippocampus is clearly an example of a distributed memory system, it is not uniformly distributed: accumulating examples show gradients and discontinuities spanning its long (dorsal-ventral) and lateral (proximal-distal) axes. Just as the subfields are specialized, so different components of episodic memories may be processed by different portions of the hippocampus.

The dorsal hippocampus receives input from the cells of the dorsolateral MEC with highest resolution grid firing patterns, while the ventral hippocampus has significant reciprocal connections with more emotionally-related neural circuits, such as the amygdala, lateral septum, and ventral subiculum. Based on these anatomical differences it has been suggested that the dorsal hippocampus serves a more spatial/navigational role, while the ventral hippocampus is preferentially associated with emotional behaviors (e.g. [99], but see [100]). Directed lesion experiments support this hypothesis, with damage to more dorsal portions of the structure impairing spatial memory, while ventral lesions leave this function intact. Recent physiological recordings in CA3 lend further support; place fields in the dorsal hippocampus were found to be more spatially specific than those in the ventral tip of the structure, which contained more non-spatial and goal-related responses [94, 95].

CA1 can also be subdivided along the proximal (adjacent to CA2) to distal (adjacent to subiculum) axis based on the input from the EC, with proximal pyramidal cells receiving input

exclusively from the MEC, while distal pyramidal cells receive input exclusively from the LEC. Directed recordings across this CA1 axis in freely-behaving rats have revealed that anatomy does predict function, with proximal pyramidal cells showing greater spatial specificity and distal cells show increased responsivity to non-spatial cues, such as objects place in the environment [89, 90].

Finally, there are also changes in intrinsic hippocampal connections along the dorsal/ventral axis. In the rat, intra-CA3 (as opposed to CA3-CA1) recurrent connections are particularly dominant in ventral hippocampus [101] – yet another indication of longitudinal, dorsal-ventral gradients in hippocampal connectivity, and an important reminder that 2D slices must ultimately be related to the 3D context of the *in vivo* brain. Back-projections from CA3 to DG also vary in density and targets along the longitudinal axis, becoming increasingly prevalent in ventral hippocampus [102] and further confounding views of the hippocampal circuit as a single loop. This complex connectivity – along with data generated using increasingly pathway-specific interventions – make it clear that we must consider the contribution of the multiple embedded circuits that begin in the EC and converge in CA1 if we are to appreciate a wider, integrated view of information processing in the structure.

Box 2: Genes in circuits

The era of genomics has ushered in an overwhelming amount of new "genotomic" data that both confirms many longstanding beliefs about hippocampal organization, as well as introduces some intriguing new twists to add to the models. Specifically, the technique of high-throughput *in situ* hybridization has made it possible to compare the expression patterns of hundreds to thousands of genes across the subfields of the structure. These studies have shown that the pyramidal cells in CA3, CA2, and CA1 have distinct molecular identities, and while it remains difficult to make the leap from protein to computation, the data largely agrees with Cajal's original boundaries of the CA fields [48, 103](Figure I).

A recent study [104] used a similar approach to address genetic diversity across the dorsal/ventral axis of the hippocampus, identifying three clear domains of differential gene expression across CA1: dorsal, intermediate and ventral, with the ventral domain further divided into 4 distinct subdomains based on gene expression gradients. Further, this data added yet another axis to consider in CA1, that of the cell type diversity within the region across the laminar axis of the pyramidal layer. While historically treated as a homogenous layer, the pyramidal cell layer does exhibit variations in thickness and organization. Gene expression data suggests that the neurons in the densely-packed superficial pyramidal layer are distinct from the sparser deep layers in dorsal CA1 [104]. While standard extracellular recording techniques preclude accurate discrimination of these cell subclasses to address possible differential functions, combinations of emerging genetic, optical and *in vivo* intracellular recording techniques may soon make this possible [105-108]. This study also determined that gene expression patterns across connected structures were similar [104]; for example the genetic

profile of a ventral CA1 neuron was more similar to neurons in the emotional regions of the brain (amygdala, lateral septum, ventral subiculum), than that of a dorsal CA1 neuron.

Genetic similarity may also define selective connections across the trisynaptic network from DG to CA1. Two independent transgenic lines, generated from identical constructs in which green fluorescent protein (GFP) expression was under the control of the Thy1.2 promoter, but distinguished by differing random genomic integration sites, demonstrated distinct developmental expression patterns [109]. The difference in timing of expression onset between the lines led to the labeling of distinct subsets of excitatory neurons across all three subregions of the hippocampus. Intriguingly, these subsets showed an extremely high degree of selective connectivity; early born granule cells in the DG were observed to be much more likely to contact early-born CA3 pyramidal cells, which in turn were more likely to synapse onto early born CA1 pyramidal cells, with the same pattern emerging for the later-born cells. This suggests the trisynaptic loop may in fact consist of parallel microcircuits, with similar neurons in a given subfield defined not by the place they sit, but rather by the time they were born.

Box3: Inhibitory influences

Default views of EC-hippocampal connectivity tend to focus on excitatory, glutamatergic connections, but feed-forward and feedback inhibition is central to modulating network activity and shaping information processing under physiological conditions. For example, in addition to synapsing onto apical dendrites of granule cells, the PP-DG projection from MEC also drives fast-spiking, GABAergic interneurons in DG [110]. Granule cells and their surrounding interneurons are tuned to respond differentially to particular oscillatory frequencies of input from EC [110], hence the net impact of PP input on GC firing could be adaptively filtered according to its pattern and does not depend solely on excitation. Models suggest that filtering of this kind by dynamically tuned inhibition may be used to divert information via different routes during different behavioral states [111, 112]. For example, novelty induces a significant increase in the firing rates of inhibitory interneurons in the DG and a slight decrease in granule cell firing rates [113]. Although speculative, this may relate to altered, acetylcholine-modulated resonance properties in EC grid cells [114] and therefore altered DG filtering in response to novelty, steering the DG-CA3 network towards separation during encoding

Inhibition also shapes the DG-CA3 interactions that contribute to the propagation and transformation of grid cell and place cell firing patterns during mnemonic processing. The majority of GC mossy fiber axons target GABAergic interneurons in CA3 [115], thus DG can have a net inhibitory effect on CA3 during some behavioral states [116], and only granule cell bursts break through and drive CA3 pyramidal cells – this gating mechanism has been called a conditional detonator [117]. Furthermore, CA3 pyramidal cells send reciprocal back-projections

to DG GABAergic interneurons (as well as excitatory mossy cells in the hilus and granule cells themselves), meaning CA3 can exert a net feedback inhibitory effect on DG [118]. Reciprocal DG-CA3 loops are certainly likely to be central to iterative processing during pattern separation and completion [4, 119], and present another example in which the likelihood and direction of information flow is critically and dynamically dependent upon excitatory-inhibitory tuning. The roles of CA2 in this routing are yet to be explored, but the unique connectivity of its interneuronal populations [57, 58] mean its inhibitory influence over CA3 and CA1 must be considered alongside its excitatory projections.

Box 4: CA2 in disease

Hippocampal dysfunction contributes to learning and memory impairments in a range of neuro-psychiatric disorders but – as in normal cognition – the precise contributions of different hippocampal subfields remain poorly defined. Increasing resolution of non-invasive imaging techniques is one factor that will help to resolve this issue, but there exist a number of indications that CA2 pathology reflects its distinct physiology and potentially unique contributions to cognition.

• **Epilepsy**. CA2 is more resistant to cell loss following clinical or experimentally-induced seizures relative to other subfields [120, 121], potentially because of its expression of adenosine A1 receptors [50] and their anticonvulsant properties [122]. Some species of rodent may even be seizure-resistant due to unique CA2 cytoarchitecture [123]. Cell loss in CA2 is decorrelated from DG cell loss in medial temporal lobe epilepsy [124], consistent with CA2's unique connectivity within hippocampal circuits allowing decoupling from the DG-CA3-CA1 loop.

• **Neurodegenerative diseases**. Although Alzheimer's disease (AD) is well-established to be associated with widespread reductions in hippocampal volume, at least one study has indicated that loss of interneurons in AD is more prevalent in DG and CA1-2, rather than CA3 [125]. It is possible that CA2 volume reduction distinguishes AD from Mild Cognitive Impairment (MCI), since a selective reduction in the CA1-2 border region has been reported in MCI [126], indicative of CA2's importance in cognitive processing. Although widespread beyond the hippocampus, alpha-synuclein and tau deposition in CA2 relative to other hippocampal

subfields have also been preferentially associated with hallucinations and dementia in Parkinson's disease [127, 128].

• **Schizophrenia**. Whilst schizophrenia is associated with dysfunction in a vast array of cortical and subcortical regions, it is clear that hippocampal abnormalities contribute to symptoms and are consistently highlighted in functional and post-mortem studies (e.g. [129]). The original finding consistent with a preferential involvement of CA2 showed profound loss of parvalbumin immunoreactivity (a marker of specific subclasses of interneurons) in this subregion [130], replicated in [131, 132], although decreases in parvalbumin immunoreactivity outside the hippocampus are widespread [133]. Relative to other hippocampal subfields, binding assays have shown reduced AMPA [134] and histamine H3 receptor binding [135] in CA2 of patients diagnosed with schizophrenia and bipolar disorder respectively , and together these histological and neurochemical abnormalities may manifest as morphological changes at the structural level [136]. Quite how CA2 dysfunction may contribute to particular positive, negative or cognitive symptoms of schizophrenia remains unclear, but the latter may be linked with altered filtering of mnemonic information in hippocampus.

Box 5. Outstanding questions

- What are the functional impacts of CA2 lesions?
- What are the spatial coding properties of CA2 neurons in vivo?
- How do the typical hippocampal local field potentials (theta, gamma, ripples) manifest in CA2 during distinct behavioral states?
- What is the impact of neuromodulation on the multiple individual circuits between the EC and CA1?
- What are the functional roles of proteins preferentially expressed in CA2?

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Figure 1:

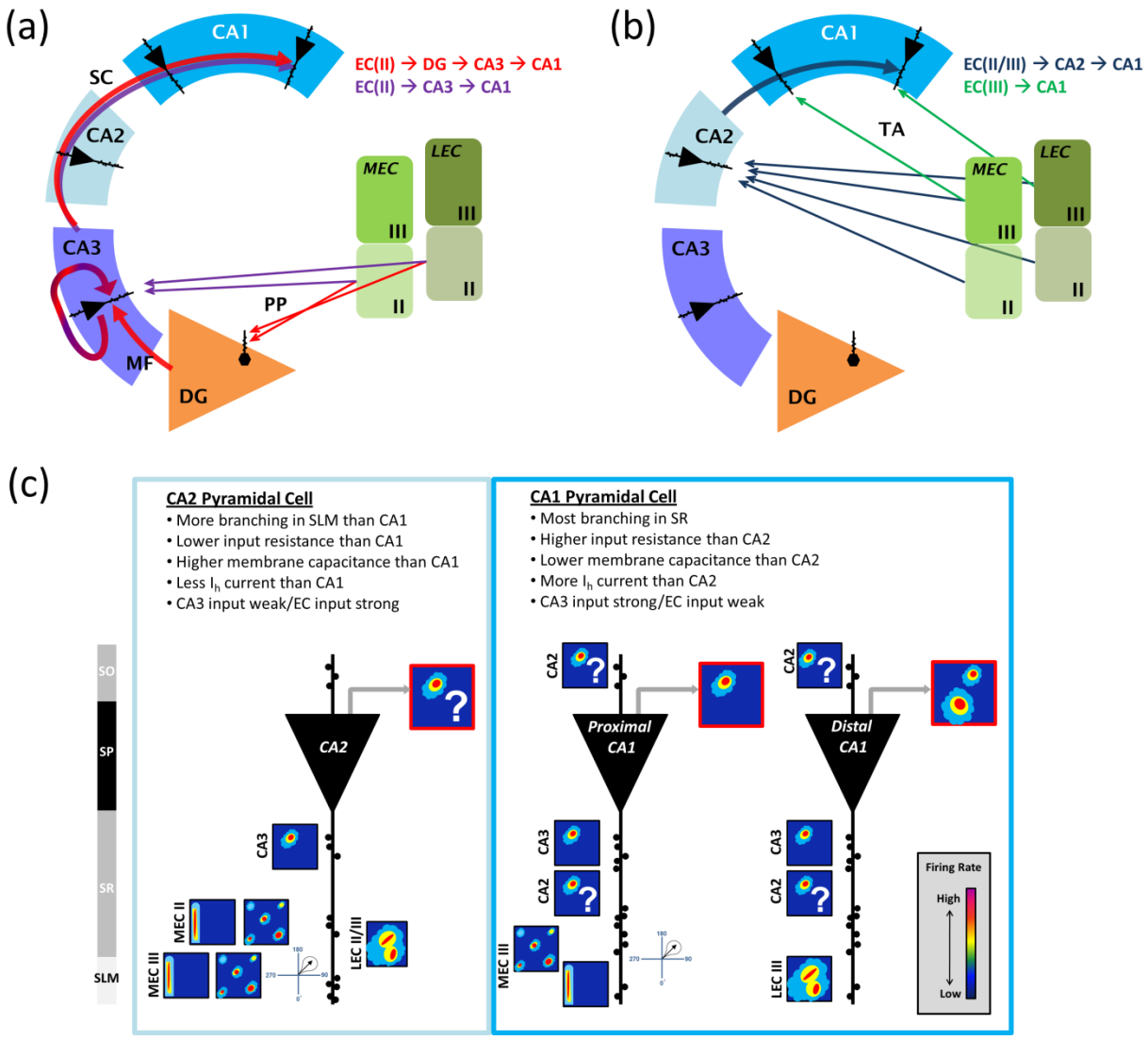
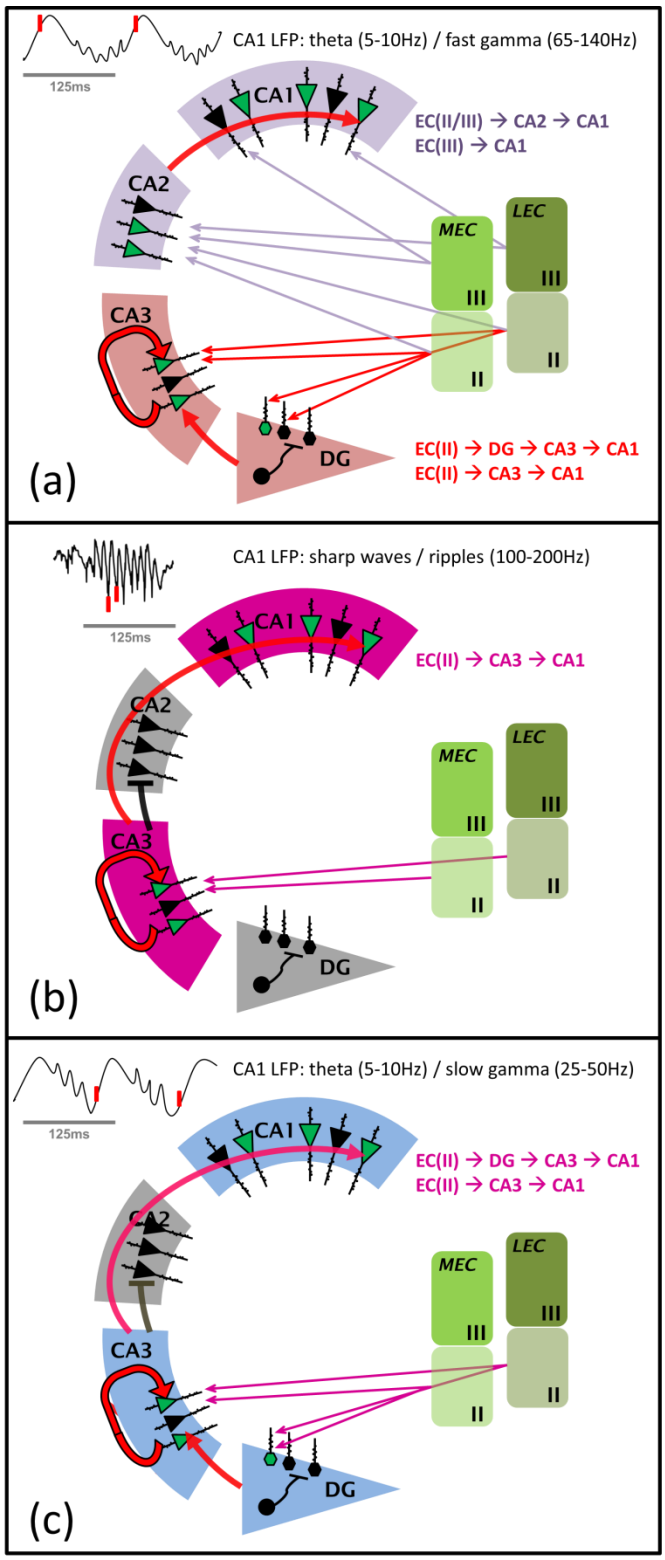

(a)
CA1
SC
CA2
CA3
MF
DG
PP
MEC
LEC
III
II
EC(II) → DG → CA3 → CA1
EC(II) → CA3 → CA1
(b)
CA1
CA2
CA3
DG
TA
MEC
LEC
III
II
EC(II/III) → CA2 → CA1
EC(III) → CA1
(c)
CA2 Pyramidal Cell
• More branching in SLM than CA1
• Lower input resistance than CA1
• Higher membrane capacitance than CA1
• Less I_h current than CA1
• CA3 input weak/EC input strong
CA1 Pyramidal Cell
• Most branching in SR
• Higher input resistance than CA2
• Lower membrane capacitance than CA2
• More I_h current than CA2
• CA3 input strong/EC input weak
SO
SP
SR
SLM
CA2
CA3
MEC II
MEC III
LEC II/III
Proximal CA1
Distal CA1
LEC III
Firing Rate
High
Low

Figure 2:


CA1 LFP: theta (5-10Hz) / fast gamma (65-140Hz)
125ms
CA1
CA2
CA3
DG
MEC
LEC
III
II
EC(II/III) → CA2 → CA1
EC(III) → CA1
EC(II) → DG → CA3 → CA1
EC(II) → CA3 → CA1
(a)
CA1 LFP: sharp waves / ripples (100-200Hz)
125ms
EC(II) → CA3 → CA1
(b)
CA1 LFP: theta (5-10Hz) / slow gamma (25-50Hz)
125ms
EC(II) → DG → CA3 → CA1
EC(II) → CA3 → CA1
(c)

Box 2, Figure 1: